

group classed as septic was that of a 79-year-old patient whose wound discharged serosanguineous fluid four days after a left hemicolectomy. The fluid grew *Streptococcus viridans*, and the wound was therefore regarded as septic.

No sensitivity reactions were encountered, and no significant side-effects were noted among the treated patients. There was no perceptible difference in the rate of wound-healing between the two groups.

Discussion

If the large bowel is opened at operation some degree of contamination of the wound can occur in spite of careful technique. Our control series suggests that at least one in five such patients will develop a septic wound.

This problem can be attacked in three ways. Firstly, an attempt can be made to render the bowel contents "sterile" by an orally administered antibacterial agent. It is clear that this cannot be achieved in all cases (Hayward, 1959) even if the sensitivities of the patients' faecal flora are known beforehand (Gunn and Gould, 1965). In addition, pharmacological toxicity is common, and there is a small but definite risk of superinfection with a resistant organism.

Secondly, systemic antibiotics can be given prophylactically after operation. Careful clinical trials have shown this measure to be ineffective (Garrod, 1955b; Pulaski, 1959), probably because of failure to appreciate the critical importance of the biochemical interaction between bacteria and host tissue in the first few hours after contamination (Burke, 1961). Though systemic antibiotics given intravenously during operation may be effective, it seems to be taking a sledgehammer to crack a nut when the problem is initially confined to the surface of the abdominal wound.

Thirdly, antibacterial substances can be placed in the wound at the time of operation. Flavine-sulphonamide powders, penicillin, and other antibiotics have been used in this way, but for one reason or another they have proved disappointing. Strong claims have been made for combined antibiotics in aerosol form (usually polymyxin, neomycin, and bacitracin), but published

clinical trials have been inadequately controlled (Gibson, 1958; Forbes, 1961). Further, the aerosol method deposits only a small quantity of the antibiotic on the wound, the remainder being dispersed into the air.

The present trial shows that ampicillin in powder form prevents wound sepsis in large-bowel surgery. Because of its low toxicity, ampicillin can be used in fairly large quantities, allowing a high local concentration. This may inhibit strains of *Escherichia coli* and other organisms resistant in vitro to the lower concentrations achieved with systemic therapy. There should be no risk of superinfection with resistant organisms elsewhere in the patient.

Summary

Seventy patients undergoing operations on the large bowel were divided by random selection into two groups. In one group the use of topical powdered ampicillin in the main abdominal wound was associated with a significant reduction in wound sepsis. No side-effects were noted.

Our interest in the problem of wound sepsis was stimulated and encouraged by Mr. T. Rowntree. Dr. J. M. Graham gave us valuable advice on the bacteriological aspects. We wish to record our thanks to Mr. S. N. Lytle and Mr. G. St. J. Hallett, who operated on a number of the patients. Dr. E. Knudsen, of Beecham Research Laboratories, provided specially packaged supplies of ampicillin.

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Prolapsed Cord

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Traditionally, prolapse of the umbilical cord has been associated with a high foetal mortality. Ten years ago it was estimated that 1,750 infants were lost annually in England and Wales from cord prolapse (Rhodes, 1956).

In 1963 there were nearly 15,000 stillbirths among 869,000 total deliveries in England and Wales (Ministry of Health, 1966). On the assumption that cord prolapse occurs once in every 300 deliveries and that the perinatal mortality is 30%, a figure reported in many series, then nearly 900 infants were lost from cord prolapse in 1963, equivalent to nearly 6% of all stillbirths.

A policy of immediate delivery in cases of prolapsed cord has greatly reduced the perinatal mortality, and the estimate of the size of the problem in 1956 and in 1963 may well be excessive.

The 50 consecutive cases of cord prolapse reported here were managed by the obstetric department of St. Mary's Hospital,

Portsmouth, between May 1964 and April 1966. For several years there has been an anaesthetist on duty solely for the obstetric department, and this anaesthetic service, combined with the provision of an operating-theatre in the labour ward, has resulted in one of the lowest perinatal mortality rates ever recorded in cases of prolapsed cord.

Comparison of these recent results with those obtained between 1948 and 1954 shows a great improvement in foetal salvage.

Results

Between May 1964 and April 1966 there were 50 cases of cord prolapse in 7,948 deliveries, giving an incidence of 1 in 159 (0.6%). Approximately half the deliveries in the area served by the hospital take place in the hospital and so the incidence in the area is probably nearer 1 in 300 deliveries. A total of seven infants were lost—five stillborn and two neonatal

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deaths—giving an uncorrected perinatal mortality of 14%. Two of the infants were abnormal, with gross anomalies incompatible with life, and a third weighed only 2 lb. 7 oz. (1,105 g.). Apart from these three, the corrected perinatal mortality attributable to cord prolapse in the series is 8%. There were no maternal deaths in this group.

Predisposing Factors

Many factors have been quoted as predisposing to cord prolapse, including surgical induction, pelvic tumours, hydramnios, low placental implantation, and obstetric manipulations. In this series none of these conditions played a significant part.

Presentation.—The presentation in these cases is shown in Table I. Breech presentation featured in 50% of the cases and carried a good foetal prognosis. The vertex was engaged in 24%, and this group accounted for five of the seven perinatal deaths.

TABLE I

Presentation	Total No.	%	Perinatal Deaths
Vertex engaged ..	12	24	5
" not engaged ..	11	22	0
Breech flexed ..	19	38	1
" extended ..	6	12	1
Transverse ..	2	4	0

Birth Weight.—The baby weighed 5½ lb. (2,500 g.) or less in 11 cases. Three deaths occurred in this group; two of these babies were abnormal, weighing 4½ lb. (2,050 g.), and one weighed only 2 lb. 7 oz. (1,105 g.). Of the remaining 39 babies weighing between 5½ and 10 lb. (2,500 and 4,535 g.) four died in the perinatal period.

Multiple Pregnancy.—There were seven cases of twin pregnancy in the series, and in five the cord of the first twin was involved.

Place of Prolapse

Home.—In 13 cases cord prolapse occurred at home, and in this group there were 11 survivors. In one case the flying squad was called to a multigravid patient. Pregnancy had been concealed and there had been no antenatal care. The general practitioner had been called to the patient—described as a case of severe abdominal pain—and found a foot and a long loop of pulsating cord protruding from the vulva. The cervix was almost fully dilated and breech extraction was carried out. The infant, a live male, weighed 8 lb. 1 oz. (3,655 g.) and needed no resuscitation. It would seem that the cord had been outside the vulva for at least one and a half hours before delivery. Of the two infants lost, in one case the foetal heart was not heard on admission and five hours later a grossly abnormal female infant delivered spontaneously as a breech. In the other case the patient was admitted in premature labour at 32 weeks with twins. The cervix was fully dilated, and the vertex engaged with a prolapsed loop of pulsating cord. Five minutes after admission spontaneous delivery of the first twin occurred. Endotracheal intubation and intermittent positive-pressure respiration was required to resuscitate the baby, which weighed only 2 lb. 7 oz. (1,105 g.) and died after seven hours.

Hospital.—In 37 cases the cord prolapsed in hospital and five infants were lost. Four were fresh stillbirths, the foetal heart was not heard in labour and vaginal examination revealed the cord prolapse. In all these four cases the foetal head was engaged. In the fifth case the infant died 25 minutes after delivery by caesarean section, the cause of death being multiple severe congenital abnormalities.

Treatment

The treatment depended on the presence or absence of foetal heart sounds and the cervical dilatation when the diagnosis was made. The results are shown in Table II.

TABLE II

Cervical Dilatation	Method of Delivery	No.	Perinatal Deaths
Fully dilated (22 cases)	Forceps	9	1 stillbirth—foetal heart not heard before delivery
	Breech extraction and assisted breech delivery	11	1 stillbirth—foetal heart not heard when diagnosis made. 1 neonatal death—prematurity
	Spontaneous delivery	2	
Not fully dilated (28 cases)	L.S.C.S.	22	1 neonatal death—abnormal infant
	Breech extraction	3	3 stillbirths—foetal heart not heard when diagnosis made in all 3 cases. 1 abnormal infant
	Spontaneous delivery	3	

The detection–delivery interval, when the cord prolapsed in hospital, or the admission–delivery interval, when cord prolapse occurred at home, averaged 14 minutes for vaginal delivery and 24 minutes for caesarean section.

Resuscitation.—Five infants required endotracheal intubation and intermittent positive-pressure respiration for resuscitation. No special measure was necessary in the remainder.

Discussion

It is interesting to compare the results of these recent cases with a similar number of cases occurring between October 1948 and July 1954 in the same unit. During that time there were 11,132 deliveries and 47 prolapsed cords, an incidence of 1 in 237 (0.4%). There were 22 stillbirths, giving a gross perinatal mortality of 46.8%. Exclusion of one premature infant under 2,500 g. leaves the corrected perinatal mortality as 44.7%. There were eight caesarean sections, an incidence of 17%. Table III gives the results from some recently reported series.

TABLE III

Year	Author	No. of Cases	Incidence (%)	Corrected Perinatal Mortality (%)	Caesarean Section Rate (%)
1951	Cope ..	350	0.59	27.9	12.0
1951	Fenton and D'Esopo ..	216	0.35	28.9	3.5
1951	Cox ..	35	0.54	11.4	37.1
1956	Rhodes ..	83	0.54	52.0*	6.0
1960	Seligman ..	100	0.4	28.0*	28.0
1961	Cushner ..	424	0.48	41.7	8.7
1961	Ball <i>et al.</i> ..	82	0.3	16.6	35.4
1961	Winch and Claman ..	55	0.1	23.0	23.0
1962	Price { 1940–50 ..	40	0.15	50.0	12.5
1962	Price { 1950–8 ..	36		14.0	25.0
1962	MacLavery and Scioscia ..	110	0.43	12.5	16.3
1962	Campbell ..	15	0.79	0.0	60.0
1962	Kurty and Munro ..	181	0.21	16.5	27.6
1963	Nelson and Burns ..	53	0.3	20.5	39.6
1963	Widholm and Nieminen ..	309	0.41	10.4	20.6
1963	Le Dall ..	100	0.67	30.4	31.0
1963	Dumont ..	52	0.21	30.0	5.7
1964	Sinnathuray ..	66	0.87	21.2	42.4
1965	McPherson ..	39	0.43	18.0	25.0
1966	Portsmouth { 1948–54 ..	47	0.4	44.7	17.0
		50	0.6	8.0	44.0

* Uncorrected perinatal mortality.

There is little doubt that rapid delivery as soon as the diagnosis of prolapsed cord is made does increase foetal salvage, especially by the use of caesarean section when the cervix is not fully dilated or nearly fully dilated. The commonest cause of death of the foetus is asphyxia, with birth trauma second when vaginal delivery is undertaken (Seligman, 1960). The asphyxia is caused by mechanical compression in some cases but possibly

more often by spasm of the umbilical cord vessels due to manipulation and cooling (Rhodes, 1956).

Various authors have commented on the adverse effect of a long detection-delivery interval on the perinatal mortality, and it has been shown that after one hour there is a rapid rise in mortality (Fenton and D'Esopo, 1951; Ball *et al.*, 1961; Winch and Claman, 1961; Nelson and Burns, 1963; Widholm and Nieminen, 1963; Sinnathuray, 1964). In a small series of 15 cases Campbell (1962) quotes an average detection-delivery interval of 8 minutes 20 seconds for vaginal delivery and 28 minutes for caesarean section. To reduce the foetal loss in prolapsed cord it is necessary to have adequate facilities, so that caesarean section or any other treatment can be initiated immediately the diagnosis is made. Routine vaginal examination as soon as the membranes rupture, irrespective of the presenting part and irrespective of its level, will favour early diagnosis and reduce the all-important time lag between the occurrence of cord prolapse and initiation of the appropriate treatment.

The late prognosis for the survivors of cord prolapse was assessed by Cushner (1961), and 95% of those located were normal. It seems that, provided the infant is delivered alive and survives the neonatal period, no harm is done by the possible period of anoxia before delivery associated with cord prolapse.

Summary

Fifty cases of cord prolapse occurring in the last two years are analysed and compared with the results obtained 12 years ago in the same unit.

Caesarean section is superior to all other forms of treatment; in the series surveyed it resulted in a very low perinatal mortality.

It is unlikely that cord prolapse will ever be eliminated as a cause of perinatal mortality.

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Preliminary Communications

Effect of Mithramycin on Calcium and Hydroxyproline Metabolism in Patients with Malignant Disease

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Mithramycin is an antibiotic with cytotoxic activity derived from an actinomycete culture belonging to the genus *Streptomyces*. The activity of the drug, like that of actinomycin D, is thought to be the inhibition of D.N.A.-directed R.N.A. synthesis (Yarbro, Kennedy, and Barnum, 1966).

The activity probably depends upon stoichiometric occlusion within the D.N.A. helix, preventing R.N.A. replication and indirectly the synthesis of protein involved in enzyme production (Goldberg, 1965). Preliminary findings in a clinical trial of mithramycin led us to anticipate disturbances in calcium metabolism which had occurred when this drug was used to treat patients with testicular malignant disease (Brown and Kennedy, 1965).

METHODS

A variety of patients with malignant disease, with and without bone metastases seen radiologically, were treated with mithramycin as part of a clinical trial (Baum and Mackay, 1966). Several patients were already in an advanced state of malignant disease, but none had a blood urea higher than 60 mg./100 ml. Patients were given a full ward diet, which did not include

excessive quantities of gelatin; their daily diet was supplemented by oral calcium galactogluconate (Sandoz) containing 760 mg. of elemental calcium. Mithramycin was given at a dosage of 25 µg./kg. in 0.45% saline by continuous infusion for eight days. In three patients (Cases 1, 4, and 6) a shorter course was given because of the onset of severe vomiting.

Twenty-four-hour collections of urine were made under toluene with added hydrochloric acid. Blood was taken before noon in each patient daily for a series of haematological and biochemical estimations. Eleven patients were treated in this way and five more had in addition 100,000 or 200,000 units of calciferol for 24 hours before and throughout treatment with mithramycin. Urine and serum were analysed for calcium by flame photometry (MacIntyre, 1961) for phosphorus (Fiske and Subbarow, 1925), while the urine was also analysed for creatinine (Nordin and Smith, 1965) and total hydroxyproline by the method of Prockop and Udenfriend (1960). Serum was also analysed for alkaline phosphatase and other enzymes, but, as no attempt was made to study bone as distinct from tumour alkaline phosphatase, the results are not included.

Owing to a degree of nausea and anorexia, fluid and food intake were reduced in a number of patients, leading to a fall in urinary output, but calcium supplements were maintained in all patients.

RESULTS

The Table shows the age, sex, type of tumour, presence of bone metastases, dose of mithramycin, initial serum calcium concentration, and 24-hour output of urinary calcium hydroxyproline. Fig. 1 shows plots of progressive changes in plasma